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Protocol for PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the emergency department (PRONTO): a multicentre open label randomised controlled trial

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Title: Protocol for PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the emergency department (PRONTO): a multicentre open label randomised controlled trial

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ABSTRACT

Introduction: Sepsis is a common, potentially life-threatening complication of infection. The optimal treatment for sepsis includes prompt antibiotics and intravenous fluids, facilitated by its early and accurate recognition. Currently, clinicians identify and assess severity of suspected sepsis using validated clinical scoring systems. In England, the National Early Warning Score 2 (NEWS2) has been mandated across all NHS trusts and ambulance organisations. Like many clinical scoring systems, NEWS2 should not be used without clinical judgement to determine either the level of acuity or a diagnosis. Despite this, there is a tendency to over-emphasise the score in isolation in patients with suspected infection, leading to the over-prescription of antibiotics, and potentially treatment-related complications and rising antimicrobial resistance. The biomarker procalcitonin (PCT) has been shown to be useful in specific circumstances to support appropriate antibiotics prescribing by identifying bacterial infection. PCT is not routinely used in the care of undifferentiated patients presenting to emergency departments (EDs), and the evidence-base of its optimal usage is poor. The PRONTO study is a randomised controlled trial in adults with suspected sepsis presenting to the ED to compare standard clinical management based on NEWS2 scoring plus PCT guided risk assessment with standard clinical management based on NEWS2 scoring alone and compare if this approach reduces prescriptions of antibiotics without increasing mortality.

Methods and analysis: PRONTO is a parallel two-arm open-label individually Randomised Controlled Trial (RCT) set in NHS EDs in the UK. Participants will be randomised in a ratio of 1:1 to standard clinical management based on NEWS2 scoring or standard clinical management based on NEWS2 scoring plus PCT guided risk assessment. This trial has two co-primary endpoints. We will compare whether the addition of PCT measurement to NEWS2 scoring can lead to a reduction in intravenous antibiotic initiation in ED patients managed as suspected sepsis, with at least no increase in 28-day mortality compared to NEWS2 scoring alone (in conjunction with local standard care pathways). The study has an internal pilot phase and group-sequential stopping rules for effectiveness and futility/safety, as well as a qualitative sub-study and a health economic evaluation.

Ethics and dissemination: The trial protocol was approved by the HRA and NHS REC (Wales Research Ethics Committee 2, reference 20/WA/0058). Findings will be disseminated through peer-reviewed journals and presented at scientific conferences.

Trial registration number: ISRCTN 54006056

Strengths of this study

- This pragmatic study aims to directly address the question of whether antibiotics can safely be given within 3 hours rather than the current one-hour target of international sepsis guidelines.
- It is designed to integrate into routine UK clinical pathways and includes assessment of acceptability and practicality in emergency department settings.
- Explicit inclusion of COVID-19 into the study design to try and reduce the amount of antibiotics administered to patients presenting with acute SARS-CoV-2 infection.

- Co-primary outcome to assess effectiveness as a stewardship intervention but also to ensure safety, combined into an innovative group-sequential design.

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Keywords: Emergency departments, sepsis, antibiotic stewardship, procalcitonin

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1] and is a medical emergency requiring prompt antimicrobial therapy and physiological support. The identification, assessment and management of sepsis is challenging because of its many non-specific symptoms and signs, which can be caused by both infectious and non-infectious diseases. In line with international recommendations, the UK National Institute for Health and Care Excellence (NICE) sepsis guidelines suggest the administration of intravenous antibiotics within an hour in patients at risk of Intensive Care Unit (ICU) admission and death [2]. However, up to 50% of patients initially managed as sepsis in the emergency department (ED) do not have a final diagnosis of sepsis [3 4] and often do not have an infection [5 6]. The current approach leads to overuse of antibiotics with the associated risk of antimicrobial resistance (AMR), antibiotic-related adverse drug reactions (e.g. *C. difficile* infection) [7], and extended hospital stays.

The challenge of delivering high quality sepsis care in an ED setting has been well recognised [8 9]. The third international consensus definition (Sepsis 3) [1] recommended use of the quick Sequential Organ Failure Assessment (qSOFA) score, to identify patients at high risk of death and prolonged ICU stay. NEWS and NEWS2 are rapid physiology-based scoring systems which are used to detect and track the deteriorating patient. NEWS has been demonstrated to have better diagnostic accuracy to qSOFA in detection of severe outcomes in sepsis [10 11]. However, with its higher sensitivity comes reduced specificity which can result in significant increased numbers of patients being managed as high risk for suspected sepsis with a corresponding pressure on ED departments. NEWS2 replaced NEWS scoring system as the standard monitoring tool in the NHS in 2019 [12] and has been found to be comparable or superior to NEWS [13-16]. In October 2021, Surviving Sepsis Campaign recommended that immediate antibiotics (within one hour) should be targeted to those with septic shock and others with suspected sepsis could wait for up to three hours for initial assessment to target antimicrobial choice or identify non-infectious mimics [17].

The emergence of COVID-19 has exacerbated this previously highlighted problem. COVID-19 is a viral infection which presents within the sepsis syndrome constellation. Secondary bacterial infections are uncommon at presentation to ED (3.5%) [19], despite this up to 83% of patients with COVID-19 received antibiotics [20 21]. NEWS2 scores are broadly predictive of COVID-19 outcome on presentation but does not appear to be predictive of bacterial co-infection [18]. Initial investigations in the ED can be helpful in distinguishing between COVID-19 and bacterial pneumonia including typical radiographic change, and COVID-19 point-of-care diagnostics [8].These results would be available within three hours for assessment and could potentially reduce unnecessary antimicrobial usage in COVID-19 management.

Procalcitonin (PCT) is a reliable biomarker that changes early in the course of bacterial infection. A recent PCT is currently the biomarker with the most available evidence to identify bacterial infections and inform antibiotic prescription decisions. Cochrane meta-analysis [9] demonstrated that the use of PCT to guide antibiotic treatment in patients with acute respiratory infections reduced antibiotic exposure and side-effects, and improved survival. Nevertheless, while the US FDA has approved PCT assays for use in sepsis, current UK NICE guidance does not recommend PCT use on the basis of insufficient evidence [22 23]. PCT predictive of outcome in COVID-19, and this may be because of its ability to identify superadded bacterial infection [10 11 24]. The available evidence suggests a low PCT will have good negative predictive value for a bacterial co-infection in cases of COVID-19 [27].

AIMS AND OBJECTIVES:

Primary Objective:

To assess whether the addition of Procalcitonin (PCT) measurement to NEWS2 scoring leads to a reduction in IV antibiotic initiation at three hours, with no increase in 28-day mortality compared to NEWS2 scoring alone in the management of patients presenting to hospital EDs in England and Wales with suspected sepsis.

Secondary Objective:

The assessment of a) feasibility, b) cost-effectiveness and c) acceptability to healthcare practitioners, patients and their family

METHODS AND ANALYSIS

Study design

PRONTO is a multi-centre, parallel two-arm, open-label, individually randomised controlled trial with two co-primary endpoints, an internal pilot phase and group-sequential stopping rules for effectiveness and futility/safety. Participants will be randomised in a ratio of 1:1 to standard clinical management based on NEWS2 scoring or standard clinical management based on NEWS2 scoring plus PCT guided risk assessment.

Internal Pilot

An internal pilot phase will be conducted over the first nine months of the recruitment period with ten lead sites. Predefined progression criteria will be used to assess feasibility to progress to the full trial,

such as site and patient absolute recruitment and consent rate, proportion of patients undergoing PCT assessments and the ability to collect co-primary outcome data.

Eligibility

Inclusion Criteria

Up to 20 EDs from across England and Wales will recruit adults (≥ 16 years) who are being managed as suspected sepsis over a 24-month period. There is no minimum NEWS2 score for inclusion into the study.

Exclusion criteria

Patients already receiving intravenous (IV) antibiotics, currently receiving myeloablative chemotherapy, patients with solid organ transplantation, allogeneic bone marrow or stem cell transplantation within 3 months prior to consent or patients known to require urgent surgical intervention at the time of randomisation.

Patients with an advance directive to withhold life-sustaining treatment or patients not wishing to receive cardiopulmonary resuscitation (CPR) may qualify provided they receive all other resuscitative measures e.g. respiratory support and fluid resuscitation.

Study Procedures

The trial schema is shown in Figure 1.

Identification and Screening

Patients with suspected sepsis will be identified at ED triage. After initial NEWS2 scoring and assessment according to current standard of care the eligibility criteria will be assessed and if no exclusion criteria apply, patients will be enrolled into the trial and randomised. A screening log of all eligible and randomised patients will be kept at each site so that any biases from differential recruitment will be detected.

Randomisation

Participants will be individually randomised in a 1:1 ratio by delegated research staff within the ED to either to standard clinical management based on NEWS2 scoring (control) or standard clinical management based on NEWS2 scoring plus PCT guided risk assessment (intervention). We will use minimisation with NEWS2 score (≥ or < 5) and site as balancing factors and add a random element to reduce the risk of subversion[28]. This will be implemented in a secure 24-hour web-based randomisation programme controlled centrally by the Centre for Trials Research (CTR) in Cardiff. Full details are provided in the PRONTO randomisation strategy.

Trial Intervention

The BRAHMS PCT-direct reader (ThermoFisher Diagnostics Ltd, (Altrincham, Cheshire, UK) is a fully validated, CE-marked point-of-care test to determine levels of PCT in the blood. The test requires 20 µl blood which will be obtained from either venous blood during standard care procedures at triage or via a finger-prick. This will be used in combination with NEWS2 assessment of adult patients with suspected sepsis in ED, using a guidance-only algorithm for clinicians (Figure 1). The risk algorithm categorises individuals as low, medium or high risk, interpretation and management (table 1). Clinicians have oversight at all times as to whether to adhere to the algorithm As currently mandated in UK, NICE clinical guidelines and quality standard QS161 [29], urgent senior review within an hour will take place should any healthcare provider identify at least one risk factor indicating high risk of progression to severe illness or death regardless of underlying aetiology. This equates to a NEWS2 ≥ 5 or an individual having a single feature of the evidence-based 'NICE high-risk criterion'.

Risk Group	Interpretation
High	High risk of progression to sepsis. Likely benefit from immediate antibiotics (within 1 hour)
Medium	Medium risk of progression to sepsis. likely benefit from early antibiotics (within 3 hours) but consider non-bacterial sources and likely source. Allows clinical teams time to complete rapid assessment In patients with high NEWS2 but low PCT (<0.5) explicit advice to consider non-infectious causes of presentation
Low	Low risk of progression to sepsis. consider non-bacterial sources, likely source and whether requires antibiotics

Table 1 Clinical Risk Management Interpretation

Informed Consent

Research carried out in emergency situations is challenging in terms of obtaining consent. Emergency research is when treatment needs to be given urgently, and it is necessary to take urgent action for the purposes of the study. In some emergency situations people may lack capacity to give consent themselves and obtaining consent from a legal representative or consulting others is not reasonably practicable. In England and Wales, the law allows adults who lack capacity to take part in emergency research without prior consent from a legal representative or consulting others, if certain conditions are met (Medicines for Human Use (Clinical Trials) Amendment (No 2) Regulations SI 2006 2984, Mental Capacity Act s32) [30]. Given the requirement for rapid clinical assessment and treatment in the management of suspected sepsis, for this trial we will use a deferred consent model. Patients and their relatives will be informed that a study is ongoing but a lengthy consent discussion will not be had so as not to delay treatment. Should the patient or consultee wish not to take part at this point, then the decision will be respected and the patient will not be enrolled into the trial. Following randomisation an approach to obtain informed consent will be made as soon as is practicably feasible, ideally within

72 hours (Figure 2). Where a participant lacks mental capacity, a maximum of three approaches will be made. After three approaches, or if the participant is not likely to regain mental capacity, a personal consultee will be approached. In extreme circumstances, where no personal consultee can be identified, a nominated consultee will be approached. Separate informed consent will be taken for participation in the qualitative data collection. Patients who do not consent to continue in the study will be withdrawn completely from the study. A tiered consent model is used in this study and allows participants to consent to different aspects of the study. A list of consent levels is in supplementary appendix table 1.

Data Collection during primary admission

All data collection will be by electronic data capture using a bespoke database developed by the CTR and hosted by Cardiff University secure servers. It is encrypted and accessed by individual username and password. Paper copies of all case report forms (CRFs) will be available. Essential documents will be kept securely in a locked cupboard, and at the end of the trial, will be archived at an approved external storage facility for 10 years. A member of the research team in ED will undertake the data collection relating to the NEWS2 screening, trial intervention and whether clinical teams followed the intervention or standard of care risk assessment. Participants who consent to continue in the study will have daily information collected from the date of randomisation until they are discharged from hospital or until day 28, whichever is sooner. Trial data is collected from patients' health records and no trial visits occur between consent and day 28. Key follow-up data is listed in supplementary appendix table 2.

FOLLOW UP

28 Day Follow Up

Day 28 follow-ups will be conducted via telephone or in person if remains an inpatient. These will comprise an EQ-5D/5L validated questionnaire for participant or proxy completion, and a Health Economics questionnaire where patient outcomes (readmission, re-treatment, hospital-acquired infection) and use of healthcare resource (hospital admissions, outpatient parenteral antimicrobial therapy, other prescribed medicines, privately purchased over-the-counter medicines, GP and hospital outpatient attendance) will be captured. In addition, direct non-medical costs borne by patients/carers as a result of attending hospital (travel costs, childcare costs, expenses incurred while in hospital, self-reported lost earnings and other direct non-medical expenses) will be collected.

90 Day Follow Up

EQ-5D/5L questionnaires will be repeated and a shortened Health Economics questionnaire to capture any additional costs or hospital admissions since the Day 28 questionnaires will be completed.

Withdrawal

Participants have the right to withdraw from the study at any time and can request that all data collected up to that point is not used.

Safety and Pharmacovigilance

The trial population comprises unwell hospital inpatients. Events such as prolongation of existing hospitalisation, life threatening events and death are expected in this population and are recorded as part of routine data collection and therefore are not subject to expedited reporting. Serious adverse events will be reported if the event results in persistent or significant disability or incapacity or consists of a congenital anomaly or birth defect. An assessment of causality between the event and the trial intervention will be carried out by the principal investigator or delegated clinician, and then independently by a clinical reviewer. If the clinical reviewer classifies the event as probably or definitely caused by the intervention, it will be classified as a serious adverse reaction. Non-serious AEs potentially attributable to PCT test will be collected as part of routine follow up at 28 days. Any other non-serious AEs will not be collected.

Data Management

Details of data management procedures (such as checking for missing, illegible or unusual value (range checks) will be specified in the PRONTO Data Management Plan. Details of Monitoring procedures will be specified in the PRONTO Monitoring plan.

STATISTICAL ANALYSIS

Outcome Measures

The co-primary outcomes of this study are the initiation of IV antibiotics at three hours (intervention arm to be shown superior to control) and 28-day mortality (intervention arm to be shown non-inferior to control). Co-primary and secondary outcomes are listed in Table 2. Final decisions about the primary effectiveness of the intervention, using these co-primary outcomes will be made based on the decision matrix (Table 3). All outcomes will be stratified by COVID-19 diagnosis (SARS-CoV2 PCR positive or high likelihood of clinical COVID-19 as determined by a senior clinician).

Table 2: Co-primary and secondary outcomes.

Co-primary outcome measures:
• Intravenous antimicrobial initiation – binary outcome assessed at 3 hours. • 28-day mortality – binary outcome.
Secondary outcome measures:
• Time until initiation of IV antibiotic therapy. • Late IV antibiotic initiation – antibiotics commenced after 3 hours. • Number of days on IV antibiotics (during admission and total over the first 28 days). • Number of days on any antibiotic (during admission and total over the first 28 days). • Number of days on broad spectrum antibiotics (IV and oral), defined by number of days on an Access group of antibiotics as defined by WHO AWaRe Classification Database (during admission and total over the first 28 days).

- ICU admission – at any point during admission.
- Length of ICU stay.
- Length of hospital stay.
- Adverse antibiotic outcomes.
- Readmission to hospital within 90 days.
- Mortality within 90 days (and time until death).
- Health utility (EQ-5D/5L) at 28 and 90 days.
- Health resource usage.
- Feasibility of implementing PCT testing alongside NEWS2 scoring in EDs .
- Acceptability of implementing PCT testing alongside NEWS2 scoring in EDs, to patients, carers and clinicians.
- Total average cost per patient per arm and cost per gained (health-adjusted) life year.

Table 3: Decision matrix for co-primary outcomes

	Reduced antibiotic initiation	Same or more antibiotic initiation
Decreased mortality	Effective	Effective
Equivalent mortality	Effective	Not effective
Increased mortality	Not effective / harmful	Not effective / harmful

Sample Size

The sample size calculation is based on two co-primary outcomes [31] :

1. 28-day mortality, for which we want to show non-inferiority of the PCT guided assessment as compared to current standard practice, using an absolute 2.5% non-inferiority margin. Assuming a 28-day mortality of 15% in patients managed as suspected sepsis treated in the ED [3 32], this means that any increase in 28-day mortality from 15% to not more than 17.5% would be considered non-inferior. For 90% power and one-sided 5% significance level the sample size required is 7002, assuming there is no difference in 28-day mortality between arms. Our patient focus group were also consulted on the 2.5% non-inferiority margin and felt that this was acceptable if there were mechanisms to monitor trial outcomes, and if this was what was needed to provide a sample size which would ensure the trial could be completed as well as answer the research question.
2. Initiation of antibiotics treatment, for which we want to show superiority. Currently around 90% of patients managed as suspected sepsis receive antibiotics (Liverpool University Hospitals NHS Foundation Trust, unpublished data). A reduction to 80% would be considered a success. To detect such an effect with 90% power and two-sided 5% significance level the sample size required is 532, which is substantially lower than what is needed for the non-inferiority endpoint. With 7002 patients we would be able to detect effects as small as a reduction from 90% to 87.6%, with 90% power.

Accounting for 5% dropout, we would need a total sample size of 7372. The group-sequential design with O'Brien-Fleming stopping boundaries for both effectiveness and futility/safety will increase the

total maximum sample size (if the study is not stopped after the interim analysis) by just over 4% to 7676 (inflated for 5% dropout).

These sample sizes were calculated using SAS 9.4 PROC POWER and PROC SEQDESIGN.

Interim analysis

A planned interim analysis of the co-primary outcomes will be conducted when 50% of patients have been recruited and followed up for 28 days. Stopping the study shall be recommended by the Independent Data Monitoring Committee (IDMC) based on group-sequential O'Brien-Fleming boundaries. They shall recommend stopping for effectiveness if:

• the PCT guided assessment is superior in terms of 28-day mortality (i.e. a significant reduction to less than 15%), or

• the PCT guided assessment is non-inferior in terms of 28-day mortality and superior in terms of initiation of antibiotics.

They shall recommend stopping for futility if the results of the interim analysis suggest futility for both endpoints. This strategy ensures overall type I error rate control [33 34]. The exact stopping rules will be specified in an interim analysis plan.

Final analysis

The primary analysis will be intention-to-treat and will fit separate two-level logistic regression models (patients nested within sites) to both co-primary outcomes (antibiotic initiation and mortality), controlling for baseline NEWS2 score (minimisation factor). The intervention will be considered effective if there is both a significant reduction in antibiotic initiation (two-sided 5% level) and if the difference in mortality between the two groups is non-inferior (one-sided 5% level). In case the 28-day mortality rate in the control arm deviates from the assumed 15%, the absolute 2.5% non-inferiority margin will be replaced with an arcsine difference 'non-inferiority frontier' [35]. The primary analysis will be adjusted to account for the group-sequential design. Imputation of missing data will be done as part of sensitivity analyses.

In a secondary analysis, complier adjusted causal effect models will be fitted to allow for non-adherence to the intervention. Two models will be fitted allowing for two different definitions of adherence:

1. Patients randomised to PCT guided care in whom a PCT test is done and the clinician considers the results as part of their decision making.
2. Patients randomised to PCT guided care in whom a PCT test is done and the clinician follows the algorithm exactly.

Analyses of secondary outcomes will also be performed as intention-to-treat and utilising appropriate two-level regression models depending on the type of outcome (e.g. linear regression for continuous outcomes, Cox regression for time-to-event outcomes) to allow for patients nested within sites. This includes an HTA and economic evaluation as per CHEERS 2022 guidance. Analyses will be split by organ system of the infection (e.g. lower urinary tract, lower respiratory, intra-abdominal, bacteraemia, skin and soft tissue etc). Stratified analyses will be undertaken at different levels of NEWS2 scoring ≤

4, 5-6 and ≥7, and will also be undertaken by COVID status. All further details will be specified in a statistical analysis plan which will be finalised prior to database lock.

Missing primary outcome data is likely to be minimal, so complete case analysis will be used. However, if this exceeds more than 20% of participants we will employ multiple imputation and report the impact on the treatment effect alongside the complete case analysis. Further detail is provided in the PRONTO Statistical Analysis Plan (SAP).

QUALITATIVE STUDY

The qualitative work will have three components: interviews with clinicians, interviews with patients/carers, and observations of trial implementation (when appropriate during the ongoing current COVID-19 pandemic). Findings will be used to aid understanding of the quantitative data and provide areas for improvement in processes to enhance the efficiency of the trial.

Interviews with clinicians will take place at two time points. Interview 1 will take place during the pilot phase and will be a semi-structured interview with 10-12 clinicians at <5 study sites (2-3 per site). This will explore the feasibility and acceptability of research processes and integration of the PCT algorithm into their ED setting. Interview 2 will be with clinicians towards the end of the trial when they have more experience of using the PCT algorithm and will identify barriers and facilitators to the use of the PCT test and algorithm in more detail, including reasons for deviating from the study algorithm.

We will conduct semi-structured interviews with patients after the 90 day follow-up, in order to gain a detailed understanding of patients' experiences of care to aid understanding of trial results. We will encourage patients to include a close family member in the interview also. This will allow us to capture an additional perspective on the patients' care.

PATIENT AND PUBLIC INVOLVEMENT

The proposal has benefited from multiple interactions with PPI groups to refine the research question and design. Author JC is a lay co-applicant/patient representative, who has co-produced and helped finalise the study design. As a co-applicant JC is a member of the Trial Management Group ensuring that all patient facing materials are presented in a suitable way. Her experience is invaluable throughout the project, including the promotion of the trial to potential participants and appropriate dissemination of findings to the lay public.

In addition, we have convened wider PPI advisory panels from both higher education institutions and NHS patient groups. We discussed the trial with the panel at the Royal Liverpool Hospital in August 2018, focusing on need, conception, design and trial management. The group fully supported the need for this trial recognising the potential for PCT measurement to improve outcomes for patients with suspected sepsis and supported the use of deferred consent. Specific feedback about these aspects has now been used to update the relevant parts of the proposal.

TRIAL MANAGEMENT

The trial is sponsored by the University of Liverpool and coordinated by Cardiff University CTR.

Trial Management Group

The Trial Management Group (TMG) will meet monthly throughout the course of the trial and will include the Co-chief Investigators, co-applicants, collaborators, trial manager, data manager and administrator. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

Trial Steering Committee and Independent Data Monitoring Committee

An independent Trial Steering Committee (TSC) consisting of an independent chairperson, two independent members and a patient representative will provide oversight of the PRONTO trial. There will also be a separate Independent Data Monitoring Committee (IDMC) to provide oversight of all matters relating to patient safety and data quality, and recommend continuing or stopping the trial depending on the results of the interim analysis. Members will be required to sign up to the remit and conditions as set out in the TSC and IDMC charters and will meet at least annually.

ETHICS AND DISSEMINATION

Research approvals

The trial was approved by the NHS Research Ethics Committee (Wales REC 2 reference 20/WA/0058) on the 21st July 2020 and subsequent HRA and Health and Care Research Wales approval was granted on 22nd July 2020.The following substantial amendments were made to the trial and were communicated to all trial sites: Amendment 5 (23rd October 2020); Amendment 7 (10th December 2020); Amendment 9 (25th February 2021); Amendment 12 (29th June 2021), Amendment 15 (15th October 2021), l Amendment 17 (6th January 2022).

The study has the following registration: **ISRCTN54006056**

Dissemination plan

We will engage with patient groups and the wider public through relevant charities such as UK Sepsis Trust and Antibiotics Action, and seek to present trial updates at their annual conferences. We will use press releases and social media outlets to publicise the trial and disseminate findings. A 90 second animation outlining the PRONTO main aims was commissioned https://www.youtube.com/watch?v=H3x-rNVlwJI [36] and accessed via posters and patient information leaflets via a scannable QR code. At the end of the trial, a final report will be prepared for the National Institute of Health Research Health Technology Assessment (NIHR HTA) Journal series. The results will be disseminated locally, nationally and internationally amongst scientific, clinical and lay groups including participants and their families. All publications and presentations related to the

trial will be authorised by the TMG in accordance with the PRONTO publication policy. Where appropriate, the results of this trial can be directly implemented in the revisions of the NICE guidelines.

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Author Contributions

NF and ST are co-Chief-Investigators of this trial. NF and ST, along with ET-J, EDC, LB-H, PH, MI-K, MJL, FM, LN, EN, PP, PS, DT-R, IW and KH led the development of the research question, study design, obtaining the funding and implementation of the protocol. JE is the Trial Manager and ET-J is the senior trial manager who coordinate the operational delivery of the trial protocol and recruitment. LB-H is the lead qualitative researcher. PP is the trial statistician. SG is the data manager. All authors listed provided critical review and final approval of the manuscript.

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Competing Interests Statement

EDC is co-CI for the BATCH Trial (HTA 15/188/42) and the PEACH study (HTA Project: NIHR132254) on PCT use, and member of NICE Diagnostic advisory committee (2014–2020), and NICE Sepsis guideline development committee (2014-6). All other authors declare no competing interests.

Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. Neither the Sponsor nor the Funder had any role in the study

design; collection, management, analysis and interpretation of data; writing of this manuscript or in the decision to submit this manuscript for publication. ThermoFisher are not funding the study, and have no influence on the design, conduct or reporting of the study

Consent for publication

Not Applicable

Availability of data and material

Not Applicable at the time of publication. Data available on request following publication of trial results.

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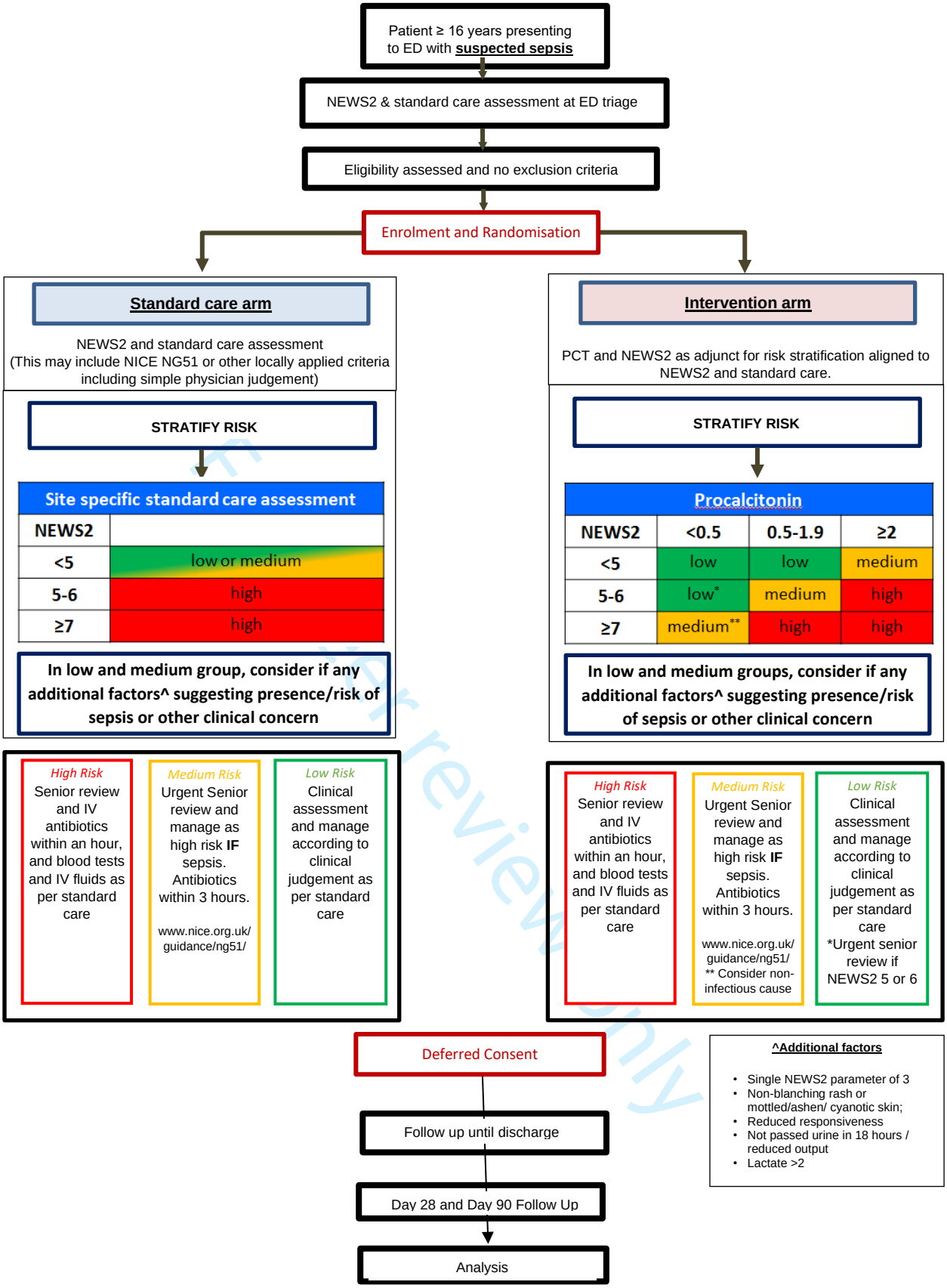
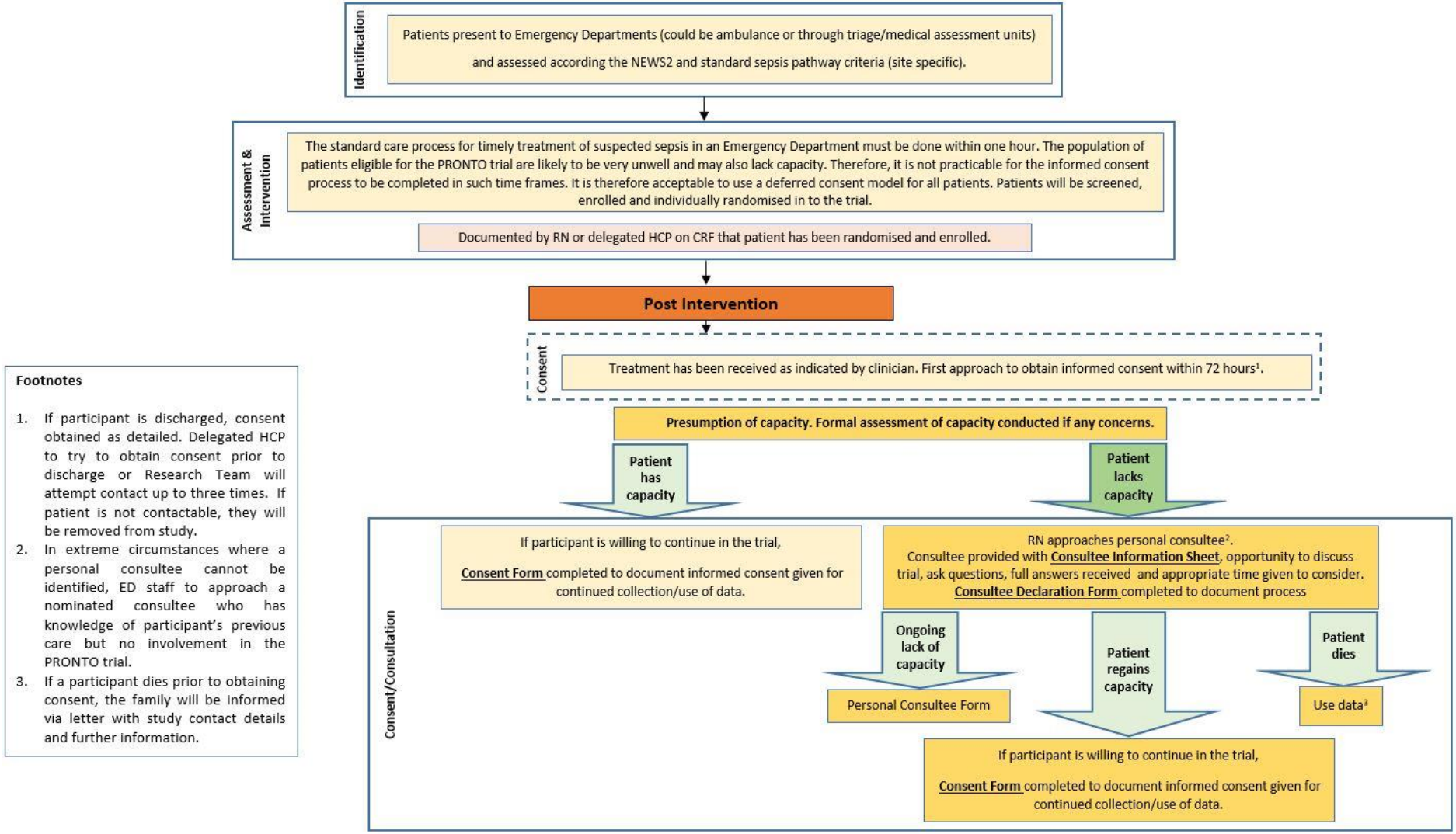
Figure Legends

Figure 1 Trial Schema

Figure 2 Informed Consent Flow Chart





Footnotes

1. If participant is discharged, consent obtained as detailed. Delegated HCP to try to obtain consent prior to discharge or Research Team will attempt contact up to three times. If patient is not contactable, they will be removed from study.
2. In extreme circumstances where a personal consultee cannot be identified, ED staff to approach a nominated consultee who has knowledge of participant's previous care but no involvement in the PRONTO trial.
3. If a participant dies prior to obtaining consent, the family will be informed via letter with study contact details and further information.

Supplementary table 1 – Tiered Consent Levels

1	Information collected as part of the trial and data from medical records up to this point can be used in the trial
2	Data from records can be collected for the 90 days of the study
3	Participant or their consultee agree to be contacted at day 28 and day 90 to ask about health, wellbeing and any further medical treatment the participant may have received
4	Information collected as part of this trial can be used in other future studies which have been approved by appropriate NHS procedures (data linkage)
5	Participant or their consultee agree to be invited to an interview about my health experiences, my views on treatment, and what it was like to take part in the PRONTO trial.

Supplementary Table 2: Outcome data collection

Outcome	Data Source	Type of data	Frequency	By Whom
Antibiotic (Abx) initiation	Observation (Obs) charts/medical notes/drug charts	Time of initiation, Abx type, dose, duration	Admission/Daily	Research Nurse
Abx use (IV and Oral) in-patient	Obs charts/medical notes/drug charts	Abx type, dose, duration	Daily	Research Nurse
Abx use (IV and Oral) post discharge up to 28 days	Obs charts/medical notes/drug charts/patient report/GP record	Abx type, dose, duration	At 28 day	Research Nurse
Adverse events	Obs charts/medical notes	Date, type	Daily	Research Nurse
ICU usage	Medical notes	Date, details of admission to ICU	Daily	Research Nurse
Unscheduled readmissions	Medical notes	ICU re-admissions, re-admissions post discharge	Daily	Research Nurse
Mortality	Medical notes	Date, Description	If before Day 28	Research Nurse
Discharge	Medical notes	Date, Description	If before Day 28	Research Nurse
Serious Adverse Drug Reactions (ADRs)	Medical notes	ADR(s)	Daily	Research Nurse
Health utility	Patient reported	-	Day 28 and Day 90	EQ-5D/5L, Patient reported questionnaire, collected by telephone or by post
Health-related Quality of Life (EQ-5D/5L)	Patient reported	-	Day 28 and Day 90	Patient reported, collected by telephone, or by post
Resource use	Patient reported	Direct medical costs and resource use	Day 28 and Day 90	Patient reported, collected by telephone, or by post

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11, 12,

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3,4, 8, 10
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4&5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9, 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	4,7,9,10,
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4,5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8,9 & supp.mat
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5,6,7 (see Figures 1 and 2)

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9-10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4, 10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a open label trial
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7, 8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__ 7, 8, __
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__ 8 - 10__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ 10_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____10_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____12_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____9_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____7_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____8_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____12_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____12_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6 and figure 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	none
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	none
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	available on request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	none

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the emergency department (PRONTO): protocol for a multicentre, open label, randomised controlled trial

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PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the emergency department (PRONTO): protocol for a multicentre, open label, randomised controlled trial

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ABSTRACT

Introduction: Sepsis is a common, potentially life-threatening complication of infection. The optimal treatment for sepsis includes prompt antibiotics and intravenous fluids, facilitated by its early and accurate recognition. Currently, clinicians identify and assess severity of suspected sepsis using validated clinical scoring systems. In England, the National Early Warning Score 2 (NEWS2) has been mandated across all NHS trusts and ambulance organisations. Like many clinical scoring systems, NEWS2 should not be used without clinical judgement to determine either the level of acuity or a diagnosis. Despite this, there is a tendency to over-emphasise the score in isolation in patients with suspected infection, leading to the over-prescription of antibiotics, and potentially treatment-related complications and rising antimicrobial resistance. The biomarker procalcitonin (PCT) has been shown to be useful in specific circumstances to support appropriate antibiotics prescribing by identifying bacterial infection. PCT is not routinely used in the care of undifferentiated patients presenting to emergency departments (EDs), and the evidence-base of its optimal usage is poor. The PRONTO study is a randomised controlled trial in adults with suspected sepsis presenting to the ED to compare standard clinical management based on NEWS2 scoring plus PCT guided risk assessment with standard clinical management based on NEWS2 scoring alone and compare if this approach reduces prescriptions of antibiotics without increasing mortality.

Methods and analysis: PRONTO is a parallel two-arm open-label individually randomised controlled trial (RCT) set in up to 20 NHS EDs in the UK with a target sample size of 7676 participants. Participants will be randomised in a ratio of 1:1 to standard clinical management based on NEWS2 scoring or standard clinical management based on NEWS2 scoring plus PCT guided risk assessment. We will compare whether the addition of PCT measurement to NEWS2 scoring can lead to a reduction in intravenous antibiotic initiation in ED patients managed as suspected sepsis, with at least no increase in 28-day mortality compared to NEWS2 scoring alone (in conjunction with local standard care pathways). PRONTO has two co-primary endpoints: initiation of IV antibiotics at three hours (superiority comparison) and 28-day mortality (non-inferiority comparison). The study has an internal pilot phase and group-sequential stopping rules for effectiveness and futility/safety, as well as a qualitative sub-study and a health economic evaluation.

Ethics and dissemination: The trial protocol was approved by the HRA and NHS Research Ethics Committee (Wales REC 2, reference 20/WA/0058). In England and Wales, the law allows the use of deferred consent in approved research situations (including emergency department studies) where the time dependent nature of intervention would not allow true informed consent to be obtained. PRONTO has approval for a deferred consent process to be used. Findings will be disseminated through peer-reviewed journals and presented at scientific conferences.

Trial registration number: ISRCTN54006056.

Strengths and limitations of this study

- Sepsis has a problem with both over and under diagnosis, and a major strength of PRONTO is the use of co-primary outcomes to assess effectiveness as an antimicrobial stewardship intervention but also to ensure safety which is vital for widespread clinical adoption of this intervention.

- PRONTO is designed to integrate into routine UK clinical pathways and includes assessment of acceptability and practicality in emergency department settings.
- Limitations of the study design include the intervention being a change in risk assessment rather than a formal prescribe/don't prescribe rule for antibiotic use, which could lead to higher rate of clinician preference in the study.
- The use of deferred consent also has the potential to increase participant withdrawal from the trial, as not all patients would have agreed to prospective informed consent.

Protocol version: PRONTO Protocol 2.1 27.01.22

Keywords: Emergency departments, sepsis, antibiotic stewardship, procalcitonin

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1] and is a medical emergency requiring prompt antimicrobial therapy and physiological support. The identification, assessment and management of sepsis is challenging because of its many non-specific symptoms and signs, which can be caused by both infectious and non-infectious diseases. In line with international recommendations, the UK National Institute for Health and Care Excellence (NICE) sepsis guidelines suggest the administration of intravenous antibiotics within an hour in patients at risk of Intensive Care Unit (ICU) admission and death [2]. However, up to 50% of patients initially managed as sepsis in the emergency department (ED) do not have a final diagnosis of sepsis [3 4] and often do not have an infection [5 6]. The current approach leads to overuse of antibiotics with the associated risk of antimicrobial resistance (AMR), antibiotic-related adverse drug reactions (e.g. *C. difficile* infection) [7], and extended hospital stays.

The challenge of delivering high quality sepsis care in an ED setting has been well recognised [8 9]. The third international consensus definition (Sepsis 3) [1] recommended use of the quick Sequential Organ Failure Assessment (qSOFA) score, to identify patients at high risk of death and prolonged ICU stay. NEWS and NEWS2 are rapid physiology-based scoring systems which are used to detect and track the deteriorating patient. NEWS has been demonstrated to have better diagnostic accuracy to qSOFA in detection of severe outcomes in sepsis [10 11]. However, with its higher sensitivity comes reduced specificity which can result in significant increased numbers of patients being managed as high risk for suspected sepsis with a corresponding pressure on ED departments. NEWS2 replaced NEWS scoring system as the standard monitoring tool in the NHS in 2019 [12] and has been found to be comparable or superior to NEWS [13-16]. In October 2021, Surviving Sepsis Campaign recommended that immediate antibiotics (within one hour) should be targeted to those with septic shock and others with suspected sepsis could wait for up to three hours for initial assessment to target antimicrobial choice or identify non-infectious mimics [17].

The emergence of COVID-19 has exacerbated this previously highlighted problem. COVID-19 is a viral infection which presents within the sepsis syndrome constellation. Secondary bacterial infections are uncommon at presentation to ED (3.5%) [18], despite this up to 83% of patients with COVID-19 received antibiotics [19 20]. NEWS2 scores are broadly predictive of COVID-19 outcome on presentation but does not appear to be predictive of bacterial co-infection [21]. Initial investigations in

the ED can be helpful in distinguishing between COVID-19 and bacterial pneumonia including typical radiographic change, and COVID-19 point-of-care diagnostics [8].These results would be available within three hours for assessment and could potentially reduce unnecessary antimicrobial usage in COVID-19 management.

Procalcitonin (PCT) is a reliable biomarker that changes early in the course of bacterial infection. A recent PCT is currently the biomarker with the most available evidence to identify bacterial infections and inform antibiotic prescription decisions. Cochrane meta-analysis [9] demonstrated that the use of PCT to guide antibiotic treatment in patients with acute respiratory infections reduced antibiotic exposure and side-effects, and improved survival. Nevertheless, while the US FDA has approved PCT assays for use in sepsis, current UK NICE guidance does not recommend PCT use on the basis of insufficient evidence [22 23]. PCT predictive of outcome in COVID-19, and this may be because of its ability to identify superadded bacterial infection [10 11 24]. The available evidence suggests a low PCT will have good negative predictive value for a bacterial co-infection in cases of COVID-19 [25].

Aims and objectives

Primary objective

To assess whether the addition of Procalcitonin (PCT) measurement to NEWS2 scoring leads to a reduction in IV antibiotic initiation at three hours, with no increase in 28-day mortality compared to NEWS2 scoring alone in the management of patients presenting to hospital EDs in England and Wales with suspected sepsis.

Secondary objective

The assessment of a) feasibility, b) cost-effectiveness and c) acceptability to healthcare practitioners, patients and their family

METHODS AND ANALYSIS

Study design

PRONTO is a multi-centre, parallel two-arm, open-label, individually randomised controlled trial with two co-primary endpoints, an internal pilot phase and group-sequential stopping rules for effectiveness and futility/safety. Participants will be randomised in a ratio of 1:1 to standard clinical management based on NEWS2 scoring or standard clinical management based on NEWS2 scoring plus PCT guided risk assessment.

Internal Pilot

An internal pilot phase will be conducted over the first nine months of the recruitment period with ten lead sites. Predefined progression criteria will be used to assess feasibility to progress to the full trial, such as site and patient absolute recruitment and consent rate, proportion of patients undergoing PCT assessments and the ability to collect co-primary outcome data.

Eligibility

Inclusion criteria

Up to 20 EDs from across England and Wales will recruit adults (≥ 16 years) who are being managed as suspected sepsis over a 24-month period. There is no minimum NEWS2 score for inclusion into the study.

Exclusion criteria

Patients already receiving intravenous (IV) antibiotics, currently receiving myeloablative chemotherapy, patients with solid organ transplantation, allogeneic bone marrow or stem cell transplantation within 3 months prior to consent or patients known to require urgent surgical intervention at the time of randomisation.

Patients with an advance directive to withhold life-sustaining treatment or patients not wishing to receive cardiopulmonary resuscitation (CPR) may qualify provided they receive all other resuscitative measures e.g. respiratory support and fluid resuscitation.

Study procedures and progress

The trial schema is shown in Figure 1.

The COVID-19 pandemic resulted in a delay to the original start date of June 2020. First participant was recruited on 20 November 2020. Current planned end date is 30 November 2022.

Identification and screening

Patients with suspected sepsis will be identified at ED triage. After initial NEWS2 scoring and assessment according to current standard of care the eligibility criteria will be assessed and if no exclusion criteria apply, patients will be enrolled into the trial and randomised. A screening log of all eligible and randomised patients will be kept at each site so that any biases from differential recruitment will be detected.

Randomisation

Participants will be individually randomised in a 1:1 ratio by delegated research staff within the ED to either to standard clinical management based on NEWS2 scoring (control) or standard clinical

management based on NEWS2 scoring plus PCT guided risk assessment (intervention). We will use minimisation with NEWS2 score (≥ or < 5) and site as balancing factors and add a random element to reduce the risk of subversion[26]. This will be implemented in a secure 24-hour web-based randomisation programme controlled centrally by the Centre for Trials Research (CTR) in Cardiff. Full details are provided in the PRONTO randomisation strategy.

Trial intervention

The BRAHMS PCT-direct reader (ThermoFisher Diagnostics Ltd, (Altrincham, Cheshire, UK) is a fully validated, CE-marked point-of-care test to determine levels of PCT in the blood. The test requires 20 µl blood which will be obtained from either venous blood during standard care procedures at triage or via a finger-prick. This will be used in combination with NEWS2 assessment of adult patients with suspected sepsis in ED, using a guidance-only algorithm for clinicians (Figure 1). The risk algorithm categorises individuals as low, medium or high risk, interpretation and management (table 1). Clinicians have oversight at all times as to whether to adhere to the algorithm As currently mandated in UK, NICE clinical guidelines and quality standard QS161 [27], urgent senior review within an hour will take place should any healthcare provider identify at least one risk factor indicating high risk of progression to severe illness or death regardless of underlying aetiology. This equates to a NEWS2 ≥ 5 or an individual having a single feature of the evidence-based 'NICE high-risk criterion'.

Table 1. Clinical risk management interpretation

Risk group	Interpretation
High	High risk of progression to sepsis. Likely benefit from immediate antibiotics (within 1 hour)
Medium	Medium risk of progression to sepsis. likely benefit from early antibiotics (within 3 hours) but consider non-bacterial sources and likely source. Allows clinical teams time to complete rapid assessment In patients with high NEWS2 but low PCT (<0.5) explicit advice to consider non-infectious causes of presentation
Low	Low risk of progression to sepsis. consider non-bacterial sources, likely source and whether requires antibiotics

Informed consent

Research carried out in emergency situations is challenging in terms of obtaining consent. Emergency research is when treatment needs to be given urgently, and it is necessary to take urgent action for the purposes of the study. In some emergency situations people may lack capacity to give consent

themselves and obtaining consent from a legal representative or consulting others is not reasonably practicable. In England and Wales, the law allows adults who lack capacity to take part in emergency research without prior consent from a legal representative or consulting others, if certain conditions are met (Medicines for Human Use (Clinical Trials) Amendment (No 2) Regulations SI 2006 2984, Mental Capacity Act s32) [28]. Given the requirement for rapid clinical assessment and treatment in the management of suspected sepsis, for this trial we will use a deferred consent model. Patients and their relatives will be informed that a study is ongoing but a lengthy consent discussion will not be had so as not to delay treatment. Should the patient or consultee wish not to take part at this point, then the decision will be respected and the patient will not be enrolled into the trial. Following randomisation an approach to obtain informed consent will be made as soon as is practicably feasible, ideally within 72 hours (Figure 2). Where a participant lacks mental capacity, a maximum of three approaches will be made. After three approaches, or if the participant is not likely to regain mental capacity, a personal consultee will be approached. In extreme circumstances, where no personal consultee can be identified, a nominated consultee will be approached. Separate informed consent will be taken for participation in the qualitative data collection. Patients who do not consent to continue in the study will be withdrawn completely from the study. A tiered consent model is used in this study and allows participants to consent to different aspects of the study (Supplementary Appendix Table 1). An example participant consent form is available in supplementary appendix.

Data collection during primary admission

All data collection will be by electronic data capture using a bespoke database developed by the CTR and hosted by Cardiff University secure servers. It is encrypted and accessed by individual username and password. Paper copies of all case report forms (CRFs) will be available. Essential documents will be kept securely in a locked cupboard, and at the end of the trial, will be archived at an approved external storage facility for 10 years. A member of the research team in ED will undertake the data collection relating to the NEWS2 screening, trial intervention and whether clinical teams followed the intervention or standard of care risk assessment. Participants who consent to continue in the study will have daily information collected from the date of randomisation until they are discharged from hospital or until day 28, whichever is sooner. Trial data is collected from patients' health records and no trial visits occur between consent and day 28. Key follow-up data is listed in supplementary appendix table 2.

Follow up

28 Day Follow Up

Day 28 follow-ups will be conducted via telephone or in person if remains an inpatient. These will comprise an EQ-5D/5L validated questionnaire for participant or proxy completion, and a Health Economics questionnaire where patient outcomes (readmission, re-treatment, hospital-acquired infection) and use of healthcare resource (hospital admissions, outpatient parenteral antimicrobial therapy, other prescribed medicines, privately purchased over-the-counter medicines, GP and hospital outpatient attendance) will be captured. In addition, direct non-medical costs borne by patients/carers as a result of attending hospital (travel costs, childcare costs, expenses incurred while in hospital, self-reported lost earnings and other direct non-medical expenses) will be collected.

90 Day Follow Up

EQ-5D/5L questionnaires will be repeated and a shortened Health Economics questionnaire to capture any additional costs or hospital admissions since the Day 28 questionnaires will be completed.

Withdrawal

Participants have the right to withdraw from the study at any time and can request that all data collected up to that point is not used.

Safety and pharmacovigilance

The trial population comprises unwell hospital inpatients. Events such as prolongation of existing hospitalisation, life threatening events and death are expected in this population and are recorded as part of routine data collection and therefore are not subject to expedited reporting. Serious adverse events will be reported if the event results in persistent or significant disability or incapacity or consists of a congenital anomaly or birth defect. An assessment of causality between the event and the trial intervention will be carried out by the principal investigator or delegated clinician, and then independently by a clinical reviewer. If the clinical reviewer classifies the event as probably or definitely caused by the intervention, it will be classified as a serious adverse reaction. Non-serious AEs potentially attributable to PCT test will be collected as part of routine follow up at 28 days. Any other non-serious AEs will not be collected.

Data management

Details of data management procedures (such as checking for missing, illegible or unusual value (range checks) will be specified in the PRONTO Data Management Plan. Details of Monitoring procedures will be specified in the PRONTO Monitoring plan.

Statistical analysis

Outcome measures

The co-primary outcomes of this study are the initiation of IV antibiotics at three hours (intervention arm to be shown superior to control) and 28-day mortality (intervention arm to be shown non-inferior to control). Co-primary and secondary outcomes are listed in Table 2. Final decisions about the primary effectiveness of the intervention, using these co-primary outcomes will be made based on the decision matrix (Table 3). All outcomes will be stratified by COVID-19 diagnosis (SARS-CoV2 PCR positive or high likelihood of clinical COVID-19 as determined by a senior clinician).

Table 2. Co-primary and secondary outcomes

Co-primary outcome measures:
• Intravenous antimicrobial initiation – binary outcome assessed at 3 hours. • 28-day mortality – binary outcome.
Secondary outcome measures:
• Time until initiation of IV antibiotic therapy.

- Late IV antibiotic initiation – antibiotics commenced after 3 hours.
- Number of days on IV antibiotics (during admission and total over the first 28 days).
- Number of days on any antibiotic (during admission and total over the first 28 days).
- Number of days on broad spectrum antibiotics (IV and oral), defined by number of days on an Access group of antibiotics as defined by WHO AWaRe Classification Database (during admission and total over the first 28 days).
- ICU admission – at any point during admission.
- Length of ICU stay.
- Length of hospital stay.
- Adverse antibiotic outcomes.
- Readmission to hospital within 90 days.
- Mortality within 90 days (and time until death).
- Health utility (EQ-5D/5L) at 28 and 90 days.
- Health resource usage.
- Feasibility of implementing PCT testing alongside NEWS2 scoring in EDs .
- Acceptability of implementing PCT testing alongside NEWS2 scoring in EDs, to patients, carers and clinicians..
- Total average cost per patient per arm and cost per gained (health-adjusted) life year

Table 3. Decision matrix for co-primary outcomes

	Reduced antibiotic initiation	Same or more antibiotic initiation
Decreased mortality	Effective	Effective
Equivalent mortality	Effective	Not effective
Increased mortality	Not effective / harmful	Not effective / harmful

Sample size

The sample size calculation is based on two co-primary outcomes [29] :

1. 28-day mortality, for which we want to show non-inferiority of the PCT guided assessment as compared to current standard practice, using an absolute 2.5% non-inferiority margin. Assuming a 28-day mortality of 15% in patients managed as suspected sepsis treated in the ED [3 30], this means that any increase in 28-day mortality from 15% to not more than 17.5% would be considered non-inferior. For 90% power and one-sided 5% significance level the sample size required is 7002, assuming there is no difference in 28-day mortality between arms. Our patient focus group were also consulted on the 2.5% non-inferiority margin and felt that this was acceptable if there were mechanisms to monitor trial outcomes, and if this was what was needed to provide a sample size which would ensure the trial could be completed as well as answer the research question.
2. Initiation of antibiotics treatment, for which we want to show superiority. Currently around 90% of patients managed as suspected sepsis receive antibiotics (Liverpool University Hospitals NHS Foundation Trust, unpublished data). A reduction to 80% would be considered a success. To detect such an effect with 90% power and two-sided 5% significance level the sample size required is 532, which is substantially lower than what is needed for the non-inferiority endpoint. With 7002

patients we would be able to detect effects as small as a reduction from 90% to 87.6%, with 90% power.

Accounting for 5% dropout, we would need a total sample size of 7372. The group-sequential design with O'Brien-Fleming stopping boundaries for both effectiveness and futility/safety will increase the total maximum sample size (if the study is not stopped after the interim analysis) by just over 4% to 7676 (inflated for 5% dropout).

These sample sizes were calculated using SAS 9.4 PROC POWER and PROC SEQDESIGN.

Interim analysis

A planned interim analysis of the co-primary outcomes will be conducted when 50% of patients have been recruited and followed up for 28 days. Stopping the study shall be recommended by the Independent Data Monitoring Committee (IDMC) based on group-sequential O'Brien-Fleming boundaries. They shall recommend stopping for effectiveness if:

• the PCT guided assessment is superior in terms of 28-day mortality (i.e. a significant reduction to less than 15%), or

• the PCT guided assessment is non-inferior in terms of 28-day mortality and superior in terms of initiation of antibiotics.

They shall recommend stopping for futility if the results of the interim analysis suggest futility for both endpoints. This strategy ensures overall type I error rate control [31 32]. The exact stopping rules will be specified in an interim analysis plan.

Final analysis

The primary analysis will be intention-to-treat and will fit separate two-level logistic regression models (patients nested within sites) to both co-primary outcomes (antibiotic initiation and mortality), controlling for baseline NEWS2 score (minimisation factor). The intervention will be considered effective if there is both a significant reduction in antibiotic initiation (two-sided 5% level) and if the difference in mortality between the two groups is non-inferior (one-sided 5% level). In case the 28-day mortality rate in the control arm deviates from the assumed 15%, the absolute 2.5% non-inferiority margin will be replaced with an arcsine difference 'non-inferiority frontier' [33]. The primary analysis will be adjusted to account for the group-sequential design. Imputation of missing data will be done as part of sensitivity analyses.

In a secondary analysis, complier adjusted causal effect models will be fitted to allow for non-adherence to the intervention. Two models will be fitted allowing for two different definitions of adherence:

1. Patients randomised to PCT guided care in whom a PCT test is done and the clinician considers the results as part of their decision making.
2. Patients randomised to PCT guided care in whom a PCT test is done and the clinician follows the algorithm exactly.

Analyses of secondary outcomes will also be performed as intention-to-treat and utilising appropriate two-level regression models depending on the type of outcome (e.g. linear regression for continuous

outcomes, Cox regression for time-to-event outcomes) to allow for patients nested within sites. This includes an HTA and economic evaluation as per CHEERS 2022 guidance. Analyses will be split by organ system of the infection (e.g. lower urinary tract, lower respiratory, intra-abdominal, bacteraemia, skin and soft tissue etc). Stratified analyses will be undertaken at different levels of NEWS2 scoring ≤ 4, 5-6 and ≥7, and will also be undertaken by COVID status. All further details will be specified in a statistical analysis plan which will be finalised prior to database lock for the planned interim analysis and subsequently published.

Missing primary outcome data is likely to be minimal, so complete case analysis will be used. However, if this exceeds more than 20% of participants we will employ multiple imputation and report the impact on the treatment effect alongside the complete case analysis.

Qualitative study

The qualitative work will have three components: interviews with clinicians, interviews with patients/carers, and observations of trial implementation (when appropriate during the ongoing current COVID-19 pandemic). Findings will be used to aid understanding of the quantitative data and provide areas for improvement in processes to enhance the efficiency of the trial.

Interviews with clinicians will take place at two time points. Interview 1 will take place during the pilot phase and will be a semi-structured interview with 10-12 clinicians at <5 study sites (2-3 per site). This will explore the feasibility and acceptability of research processes and integration of the PCT algorithm into their ED setting. Interview 2 will be with clinicians towards the end of the trial when they have more experience of using the PCT algorithm and will identify barriers and facilitators to the use of the PCT test and algorithm in more detail, including reasons for deviating from the study algorithm.

We will conduct semi-structured interviews with patients after the 90 day follow-up, in order to gain a detailed understanding of patients' experiences of care to aid understanding of trial results. We will encourage patients to include a close family member in the interview also. This will allow us to capture an additional perspective on the patients' care.

Patient and public involvement

The proposal has benefited from multiple interactions with PPI groups to refine the research question and design. Author JC is a lay co-applicant/patient representative, who has co-produced and helped finalise the study design. As a co-applicant JC is a member of the Trial Management Group ensuring that all patient facing materials are presented in a suitable way. Her experience is invaluable throughout the project, including the promotion of the trial to potential participants and appropriate dissemination of findings to the lay public.

In addition, we have convened wider PPI advisory panels from both higher education institutions and NHS patient groups. We discussed the trial with the panel at the Royal Liverpool Hospital in August 2018, focusing on need, conception, design and trial management. The group fully supported the need

for this trial recognising the potential for PCT measurement to improve outcomes for patients with suspected sepsis and supported the use of deferred consent. Specific feedback about these aspects has now been used to update the relevant parts of the proposal.

Trial management

The trial is sponsored by the University of Liverpool and coordinated by Cardiff University CTR.

Trial Management Group

The Trial Management Group (TMG) will meet monthly throughout the course of the trial and will include the Co-chief Investigators, co-applicants, collaborators, trial manager, data manager and administrator. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

Trial Steering Committee and Independent Data Monitoring Committee

An independent Trial Steering Committee (TSC) consisting of an independent chairperson, two independent members and a patient representative will provide oversight of the PRONTO trial. There will also be a separate Independent Data Monitoring Committee (IDMC) to provide oversight of all matters relating to patient safety and data quality, and recommend continuing or stopping the trial depending on the results of the interim analysis. Members will be required to sign up to the remit and conditions as set out in the TSC and IDMC charters and will meet at least annually.

ETHICS AND DISSEMINATION

Ethics approvals and consent

The trial was approved by the NHS Research Ethics Committee (Wales REC 2, reference 20/WA/0058) on the 21st July 2020 and subsequent HRA and Health and Care Research Wales approval was granted on 22nd July 2020. In England and Wales, the law allows the use of deferred consent in approved research situations (including emergency department studies) where the time dependent nature of intervention would not allow true informed consent to be obtained. PRONTO has approval for a deferred consent process to be used, full details are in Informed Consent section above. The following substantial amendments were made to the trial and were communicated to all trial sites: Amendment 5 (23rd October 2020); Amendment 7 (10th December 2020); Amendment 9 (25th February 2021); Amendment 12 (29th June 2021), Amendment 15 (15th October 2021), Amendment 17 (6th January 2022).

The study has the following registration number: ISRCTN54006056.

Dissemination plan

We will engage with patient groups and the wider public through relevant charities such as UK Sepsis Trust and Antibiotics Action, and seek to present trial updates at their annual conferences. We will use press releases and social media outlets to publicise the trial and disseminate findings. A 90 second animation outlining the PRONTO main aims was commissioned https://www.youtube.com/watch?v=H3x-rNVlwJI [34] and accessed via posters and patient information leaflets via a scannable QR code. At the end of the trial, a final report will be prepared for the National Institute of Health Research Health Technology Assessment (NIHR HTA) Journal series. The results will be disseminated locally, nationally and internationally amongst scientific, clinical and lay groups including participants and their families. All publications and presentations related to the trial will be authorised by the TMG in accordance with the PRONTO publication policy. Where appropriate, the results of this trial can be directly implemented in the revisions of the NICE guidelines.

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Contributors

NF and ST are co-Chief-Investigators of this trial. NF and ST, along with ET-J, EDC, LB-H, PH, MI-K, MJL, FM, LN, EN, PP, PS, DT-R, IW and KH led the development of the research question, study design, obtaining the funding and implementation of the protocol. JE is the Trial Manager and ET-J is the senior trial manager who coordinate the operational delivery of the trial protocol and recruitment. LB-H is the lead qualitative researcher. PP is the trial statistician. SG is the data manager. All authors listed provided critical review and final approval of the manuscript.

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Competing interests

EDC is co-CI for the BATCH Trial (HTA 15/188/42) and the PEACH study (HTA Project: NIHR132254) on PCT use, and member of NICE Diagnostic advisory committee (2014–2020), and NICE Sepsis guideline development committee (2014-6). All other authors declare no competing interests.

Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. Neither the Sponsor nor the Funder had any role in the study design; collection, management, analysis and interpretation of data; writing of this manuscript or in the decision to submit this manuscript for publication. ThermoFisher are not funding the study, and have no influence on the design, conduct or reporting of the study

Consent for publication

Not applicable.

Data availability statement

Not applicable at the time of protocol publication. Data available on request following publication of trial results.

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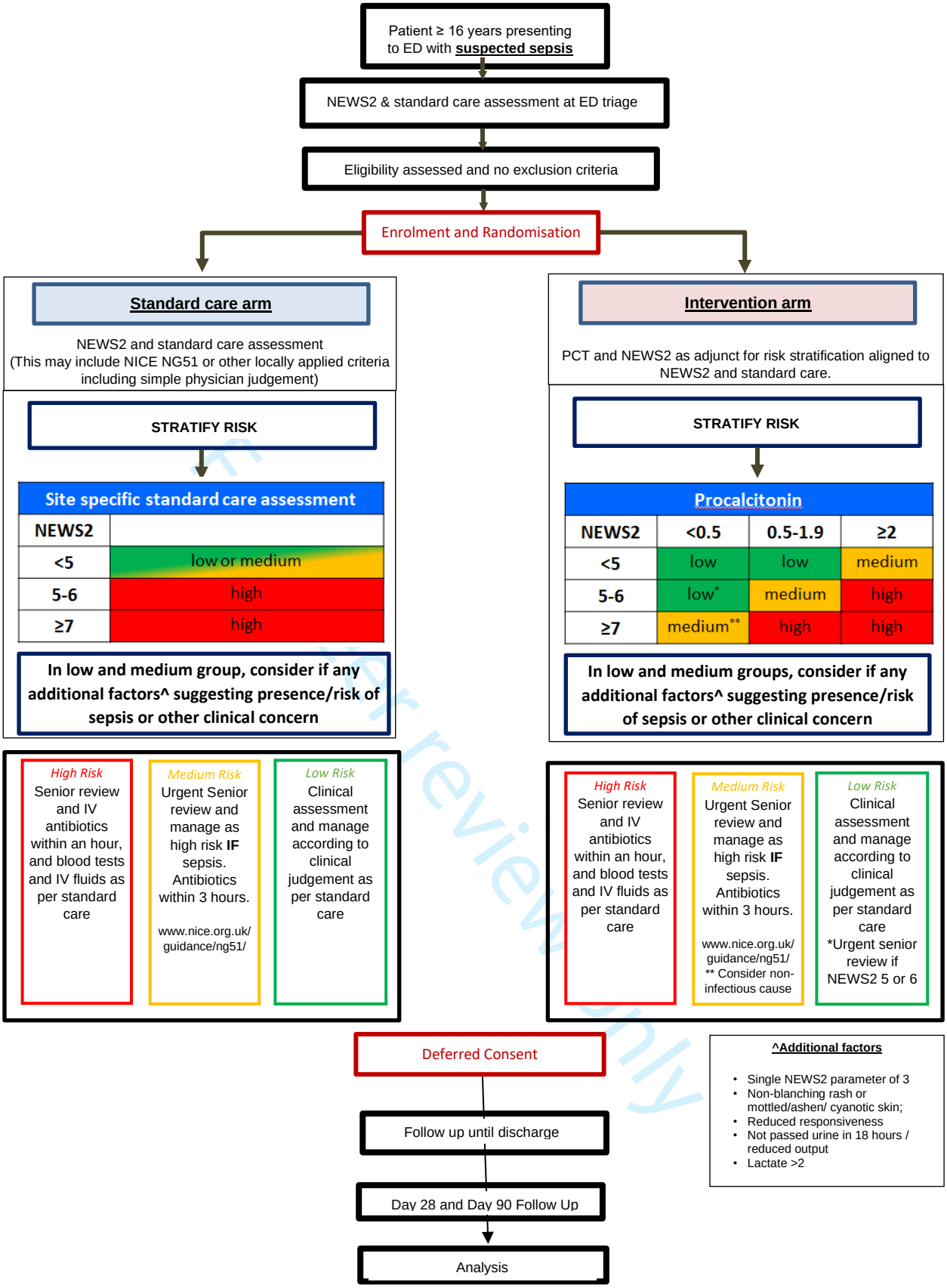
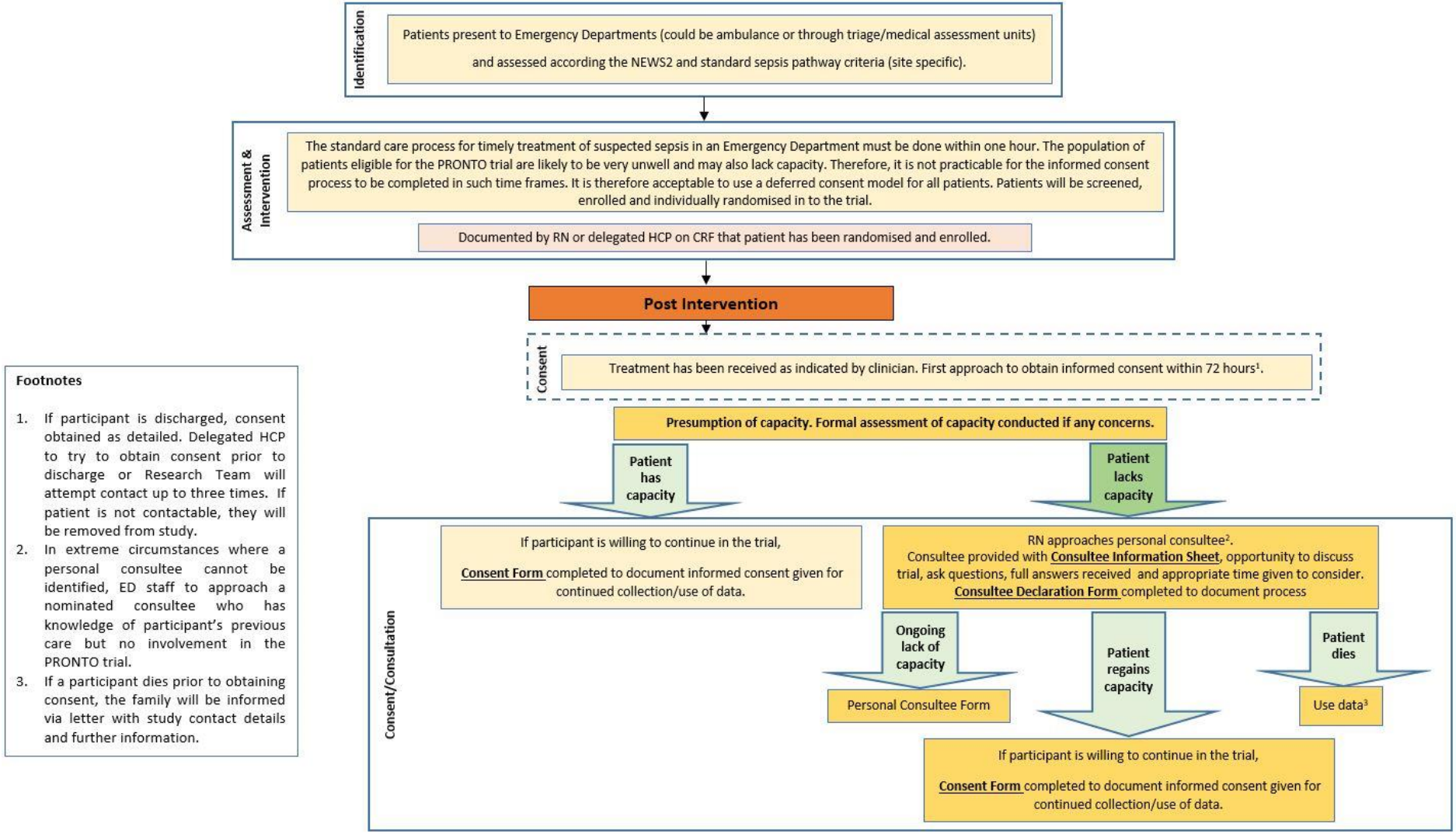
FIGURE TITLES

Figure 1. Trial schema

Figure 2. Consent procedures





Footnotes

1. If participant is discharged, consent obtained as detailed. Delegated HCP to try to obtain consent prior to discharge or Research Team will attempt contact up to three times. If patient is not contactable, they will be removed from study.
2. In extreme circumstances where a personal consultee cannot be identified, ED staff to approach a nominated consultee who has knowledge of participant's previous care but no involvement in the PRONTO trial.
3. If a participant dies prior to obtaining consent, the family will be informed via letter with study contact details and further information.

Protocol for PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the emergency department (PRONTO): a multicentre open label randomised controlled trial

Supplementary File

Supplementary table 1 – Tiered Consent Levels

1	Information collected as part of the trial and data from medical records up to this point can be used in the trial
2	Data from records can be collected for the 90 days of the study
3	Participant or their consultee agree to be contacted at day 28 and day 90 to ask about health, wellbeing and any further medical treatment the participant may have received
4	Information collected as part of this trial can be used in other future studies which have been approved by appropriate NHS procedures (data linkage)
5	Participant or their consultee agree to be invited to an interview about my health experiences, my views on treatment, and what it was like to take part in the PRONTO trial.

PROcalcitonin and NEWS2 evaluation for Timely identification of sepsis and Optimal use of antibiotics in the Emergency Department

Site ID | | | | **PID** | | | | |

PARTICIPANT CONSENT FORM

Chief Investigator: Professor Neil French, University of Liverpool

(Please **initial** each statement and sign in full at the bottom of the page)

1.	I confirm that I have read and understood the Patient Information Sheet (version 1.2, dated 08.10.2020) for the PRONTO trial. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	_____
2.	I understand that I have already entered the trial but do not have to continue to take part. I understand that I can agree to take part in different parts of the trial and will indicate my choice below. I understand that I am free to withdraw my consent at any time, without giving any reason, without my normal medical care or legal rights being affected.	_____
3.	I understand the trial is randomised and no one has picked which treatment I received. I understand that I was randomised to have either an additional procalcitonin test or standard care. If I was allocated to the treatment arm of the trial, procalcitonin levels in my blood were tested as part of routine blood tests or via an additional finger prick in the absence of routine blood collection. I consent to the data generated from the procalcitonin test to be used for the purposes of this trial.	_____
4.	I understand that information collected during the trial can be used by the study team to look at treatment of sepsis in patients presenting to the emergency department.	_____
5.	I understand that information collected about me that is held and maintained by NHS Digital and other central UK NHS bodies, may be collected from my medical records and other health-related records and looked at by the research team and responsible practitioners during the trial.	_____
6.	I understand that information collected about me (including name and address) will be held at the Centre for Trials Research, Cardiff University according to the 2018 General Data Protection Regulation (GDPR) (EU 2016/679). I understand that this information will be kept strictly confidential and that no personal information will be used in the study report or publications.	_____
7.	I agree to continue to take part in the trial**.** **Please select which aspects you agree to take part in:**	_____
8	I agree that information collected as part of the trial and data from my medical records up to this point can be used in the trial.	_____
9	I agree that data from my records can be collected for the 90 days of the study	_____

10	I agree to be contacted at day 28 and day 90 to ask about my health, wellbeing and any further medical treatment I may have received. I give my consent for a member of the research team to contact me by the following methods to complete these surveys: Telephone Email Post.	
11	I agree that the information collected as part of this trial can be used in other future studies which have been approved by appropriate NHS procedures (data linkage)	
12.	I agree to be invited to an interview about my health experiences, my views on treatment, and what it was like to take part in the PRONTO trial.	

Name of Participant: _____ Signed:_____Date:___/___/___

Name of Person taking consent _____ Signed:_____Date:___/___/___

Supplementary Table 2: Outcome data collection

Outcome	Data Source	Type of data	Frequency	By Whom
Antibiotic (Abx) initiation	Observation (Obs) charts/medical notes/drug charts	Time of initiation, Abx type, dose, duration	Admission/Daily	Research Nurse
Abx use (IV and Oral) in-patient	Obs charts/medical notes/drug charts	Abx type, dose, duration	Daily	Research Nurse
Abx use (IV and Oral) post discharge up to 28 days	Obs charts/medical notes/drug charts/patient report/GP record	Abx type, dose, duration	At 28 day	Research Nurse
Adverse events	Obs charts/medical notes	Date, type	Daily	Research Nurse
ICU usage	Medical notes	Date, details of admission to ICU	Daily	Research Nurse
Unscheduled readmissions	Medical notes	ICU re-admissions, re-admissions post discharge	Daily	Research Nurse
Mortality	Medical notes	Date, Description	If before Day 90	Research Nurse
Discharge	Medical notes	Date, Description	If before Day 28	Research Nurse
Serious Adverse Drug Reactions (ADRs)	Medical notes	ADR(s)	Daily	Research Nurse
Health utility	Patient reported	-	Day 28 and Day 90	EQ-5D/5L, Patient reported questionnaire, collected by telephone or by post
Health-related Quality of Life (EQ-5D/5L)	Patient reported	-	Day 28 and Day 90	Patient reported, collected by telephone, or by post
Resource use	Patient reported	Direct medical costs and resource use	Day 28 and Day 90	Patient reported, collected by telephone, or by post

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11, 12,

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3,4, 8, 10
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9, 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	4,7,9,10,
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4,5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8,9 & supp.mat
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5,6,7 (see Figures 1 and 2)

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____9-10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____4, 10_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____ 5_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____5_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____5_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a open label trial
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___ 7, 8_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____7-9_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__ 7, 8, __
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__ 8 - 10__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ 10_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____10_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____12_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____9-10_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____8_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____8_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____12_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____12_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6-7 and figure 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	none
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	none
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	none

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.